VIA EFS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Jonathan David CASTILE, *et al.*	§	
Conf. No.:	1809	§ Group Art Unit:	1616
Appln. No.:	10/596,817	§ Examiner:	Mina Haghighatian
Filing Date:	June 26, 2006	§ Attorney Doc. No.:	10774-87US (ARCCX/P32302US)

Title: INTRANASAL COMPOSITIONS

DECLARATION OF JONATHAN DAVID CASTILE UNDER 37 C.F.R. § 1.132

I, Jonathan David Castile, hereby declare as follows:

1. I am an inventor of the subject matter of the above-identified application.

2. My present position is Formulation Group Head, working for Archimedes Development Limited (formerly West Pharmaceutical Services Drug Delivery and Clinical Research Centre Limited), an English company, and the assignee of the present application. I have worked in the research and development of pharmaceutical formulations since 2000 to the present day.

3. I hold degrees of Bachelor of Pharmacy and Doctor of Philosophy in Pharmaceutics, both from The School of Pharmacy, University of London, United Kingdom. My *curriculum vitae* accompanies this Declaration as Exhibit A.

4. By virtue of my training and experience, I consider myself an expert with respect to intranasal drug delivery compositions, including chitosan-containing compositions, and believe that others would also consider me to be such an expert.

5. I have read and understand the present application, and am familiar with its prosecution, including the outstanding Office Action of June 10, 2010, and the Amendment in response to the outstanding Office Action, to be filed contemporaneously with this Declaration. The term "present invention" as used herein refers to the invention defined at least by independent claim 37 of the accompanying Amendment, which is directed to a composition in the form of an aqueous solution for nasal delivery of zolpidem or a pharmaceutically acceptable salt thereof, wherein the composition comprises: (a) 16 to 97 mg/ml of zolpidem (expressed as the free base); (b) sulfobutylether β-cyclodextrin (SBE-CD); and (c) chitosan, a salt, or a derivative thereof or a salt of a derivative thereof.

6. The Examiner relies upon various combinations of the following references for a conclusion that the present invention would have been obvious to a person of ordinary skill in the art at the time of its invention: Kramer et al. US Patent Application Publication No. US 2004/0241100 ("Kramer"); Auh European Patent EP 1 250 925 ("Auh"); Birch, *et al.* International Application Publication No. WO 03/080021 A2 ("Birch"), in which I am named as a co-inventor; Liu, *et al.* International Application Publication No. WO 03/095498 A1 (in Japanese) as understood based on its equivalent US Patent Application Publication No. US 2005/0215520 ("Liu"); and Loftsson, *et al.* US Patent 6,699,849.

7. As understood, in the Office Action, in essence, the Examiner combines teachings of the references as follows: From Kramer, use of zolpidem in an aqueous solution formulation for intranasal administration, with an incidental disclosure, without any examples or explicit recitation of a composition containing it, of chitosan hydroxycellulose as an example of a mucoadhesive; from Auh, a nasal spray formulation of ondansetron hydrochloride with other components such as SBE-CD as a solubiliser; from Birch aqueous formulations suitable for intanasal administration comprising buprenorphine and a pectin or chitosan; and from Liu, a sterile water-soluble complex of water-insoluble or sparingly-soluble organic medicines, including zolpidem from a long list of a great many medicines, and β-cyclodextrin derivatives. The Examiner concluded at the bottom of page 15 of the Detailed Action that the present invention is "no more than the substitution of conventional components of active agents," and therefore would have been obvious.

8. Pharmaceutical and drug delivery research is not conducted in reality as apparently considered by the Examiner, namely, in hindsight, by later picking and choosing various

ingredients from among other compositions including other drugs and other components from references, against the background of a successful invention. Instead, such research is generally conducted, and was conducted concerning the present invention, by starting with a goal, here how to better deliver zolpidem intranasally to have the desired pharmacokinetic properties ultimately achieved by the present invention after considerable experimentation in view of the unpredictable effects regarding zolpidem as the active ingredient in combination with SBE-CD and chitosan.

9. Since the effect of cyclodextrin, and particularly SBE-CD, is an issue in the present application in view of its recitation in claim 37, background information about cyclodextrins and drug delivery is believed to be important to the understanding of the present invention. The use of cyclodextrins in formulation science is well established, primarily to increase the solubility of poorly-soluble drug compounds. Cyclodextrins can increase drug bioavailability by solubilising an otherwise insoluble drug and thus delivering it to the absorption site in dissolved form. However, for a drug which has reasonable, but not high, aqueous solubility, the situation can be more complicated. Cyclodextrin molecules adopt a cone-like structure in aqueous solution, with a relatively hydrophilic (water soluble) exterior and hydrophobic interior cavity. The hydrophobic drug molecule will form an inclusion complex within the interior cavity of the cyclodextrin molecule and it will need to partition out of the cyclodextrin and, subsequently, diffuse across the mucosal membrane in order to be absorbed. Consequently, depending on the affinity between the drug and cyclodextrin molecules, it could be that absorption of drug from a cyclodextrin formulation is impaired relative to a simple solution, and although the cyclodextrin may allow a larger dose of drug to be administered, the proportion of the drug absorbed could be reduced. This means that the effect that a given cyclodextrin has on the pharmacokinetic properties of a drug will vary from one drug to another, particularly if the drugs are unrelated. Thus, information about the effect a cyclodextrin has with one drug is not predictive for another unrelated drug. Moreover, different cyclodextrins are also likely to give different effects, including pharmacokinetic effects and solubilisation potential for different molecules, in that the effects of SBE-CD are not predictable from other cyclodextrins, such as hydroxypropyl-β-cyclodextrin or randomly-methylated β-cyclodextrin.

10. The inclusion of other components, such as chitosan, into a composition containing cyclodextrins such as SBE-CD, further complicates the unpredictable nature of how a drug's pharmacokinetics may be affected when administered to a subject; for example it can be envisaged that there will be competing interactions between the different formulation components, potentially affecting the quantity of free drug available for absorption across the mucosal surface and the speed at which absorption occurs.

11. As an example of the varying and unpredictable nature of cyclodextrins and chitosan on the pharmacokinetics of drugs, Archimedes Development Limited conducted a study, under my direction and supervision, evaluating the pharmacokinetic performance of a range of intranasally-administered ondansetron formulations in sheep. Ondansetron is the active ingredient in the Auh reference. Ondansetron has relatively low aqueous solubility and cyclodextrins were used in some of the formulations in order to increase the concentration of drug which could be dissolved and thus allow the dose to be administered in a smaller volume of solution.

12. The study used the following materials, preparation and procedure, as set forth below.

Experimental

Materials

Ondansetron hydrochloride dihydrate (MW = 365.8) (ondansetron base MW = 293.4), Yick-Vick chemicals, Hong Kong.

Randomly-methylated β-cyclodextrin (RAMEB-CD) (Cavasol® W7 M Pharma), Wacker Cyclodextrins, Germany.

Chitosan glutamate (Protasan UP G213), Pronova, Drammen, Norway.

Hydroxypropyl-β-cyclodextrin (HP-β-CD), Janssen, Beerse, Belgium.

Benzalkonium chloride (BZK) 50% aqueous solution, Albright and Wilson, UK.

Ultrapure water.

Preparation of nasal formulations

Formulations were prepared with the compositions set out in Table 1 below:

Table 1

Ingredient	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Ondansetron (as HCl salt)	15 mg/ml*	40 mg/ml**	40 mg/ml**	40 mg/ml**
RAMEB-CD	--	300 mg/ml	300 mg/ml	--
HP-β-CD	--	--	--	300 mg/ml
Chitosan glutamate	5 mg/ml	--	5 mg/ml	5 mg/ml
BZK***	0.15 mg/ml	0.15 mg/ml	0.15 mg/ml	0.15 mg/ml
Water	To 100 ml	To 100 ml	To 100 ml	To 100 ml

* = 18.7 mg/ml HCl salt; ** = 49.9 mg/ml HCl salt; *** used as 7.5 mg/ml aqueous solution

Formulation 1 was prepared by dissolving chitosan glutamate in approximately 25 ml of water in a beaker. Ondansetron was weighed into a 100 ml volumetric flask and the chitosan solution added with stirring. The beaker was rinsed with water and the contents added to the flask. Benzalkonium chloride was added to the flask and the flask contents were stirred until the drug had dissolved and then made up to volume with water.

Formulations 2, 3 and 4 were prepared by firstly dissolving the cyclodextrin in approximately 30 ml of water using sonication. Where included, the chitosan glutamate was then dissolved by stirring into the cyclodextrin solution. Ondansetron was weighed into a volumetric flask and the cyclodextrin/(chitosan) solution added and the formulation completed as described for Formulation 1.

Evaluation of formulations in sheep

The formulations were tested in a cross-over study in a group of 5 sheep. For each of the nasal formulations a volume of solution equivalent to 12 mg of ondansetron was administered via a spray device modified for use in sheep. The dose was divided between each nostril. As a control for the purpose of measuring absolute bioavailability, 5 mg of ondansetron dissolved in saline was administered by intravenous injection. Following administration of the doses, blood samples were collected from each animal at regular intervals over a 240 minute period. Serum was separated from the blood and analysed for ondansetron content using an HPLC assay.

13. Pharmacokinetic parameters based on the study of paragraphs 11 and 12 were calculated from the serum data using WinNonlin software (Scientific Consulting, USA). The bioavailability of each nasal formulation in each animal was calculated using the area under the serum concentration-time curve (AUC) data generated by the software, as follows:

$$\text{Bioavailability} = \frac{\text{AUC[nasal] x dose[IV]}}{\text{AUC[IV] x dose[nasal]}} \times 100$$

Results

The mean bioavailability data for the four intranasal ondansetron formulations are provided in Table 2 below.

Table 2

Formulation	Composition	Bioavailability (% relative to IV injection)
1	15 mg/ml ondansetron + 5 mg/ml chitosan glutamate	9.4
2	40 mg/ml ondansetron + 300 mg/ml randomly-methylated β-cyclodextrin	19.0
3	40 mg/ml ondansetron + 300 mg/ml randomly-methylated β-cyclodextrin + 5 mg/ml chitosan glutamate	15.1
4	40 mg/ml ondansetron + 300 mg/ml hydroxypropyl β-cyclodextrin + 5 mg/ml chitosan glutamate	10.2

14. The resulting data of this study show that the inclusion of a cyclodextrin in an ondansetron-containing solution improved the bioavailability of ondansetron. However, when a combination of a chitosan and cyclodextrin was used, the bioavailability decreased. Thus, there was no advantage in using the combination of a chitosan and a cyclodextrin where ondansetron is the active ingredient.

15. The results of the ondansetron study of paragraphs 11-14 are significantly different from the experimental results reported in the present application, and demonstrates the unpredictable nature of the use of cyclodextrins and chitosan in combination with various drugs. Table 3 of the present application reports the bioavailability of a composition of the invention (Example 4) versus a composition using zolpidem and SBE-CD (Example 3) and an aqueous saline solution of zolpidem (Example 5). The solution of Example 4 contained both SBE-CD and chitosan glutamate and shows a significant improvement in bioavailability compared to Example 3, which contained SBE-CD but no chitosan. This is surprising and unexpected and could not have been predicted from the information about ondansetron provided in Auh or as set forth in the study of paragraphs 11-14.

16. The distinctions among drugs and their properties, including their pharmacokinetics are significant. As explained at page 3, fourth paragraph, of the present application, relatively high concentrations of zolpidem are required in order to effectively treat insomnia using a composition delivered via the intranasal route. The concentrations required are above the reported aqueous solubility of zolpidem tartrate (zolpidem hemitartrate) as published in the Merck Index, Thirteenth Edition (see accompanying Exhibit B, the title page and page 1816 that includes the entry for zolpidem). It has been found that the inclusion of SBE-CD in the compositions of the present invention enhances the aqueous solubility of zolpidem (and its salts). This means that compositions comprising zolpidem in a concentration suitable for nasal delivery for the treatment of insomnia can be provided.

17. It is particularly important when producing a composition for nasal delivery that the drug is present in the solution at a suitably high concentration. This is because, due to the nature of the nasal cavity, there is a limit to the amount of liquid that can be administered at one time. As discussed at page 13, lines 26-31, of the present application, in practical terms it is only possible to administer up to about 0.2 ml of solution to each nostril. Thus, it is necessary to ensure that sufficient drug to provide the required therapeutic effect is contained in this amount, or less, of solution.

18. It is also desirable to avoid using a saturated solution of the drug. Saturated solutions contain the maximum amount of dissolved drug possible at a given temperature. Changes in storage conditions, such as changes in temperature, can result in precipitation of the drug. This is undesirable because it could reduce the amount of drug delivered when the

solution is used. In other words, the use of a saturated solution would result in inconsistent and unreliable drug dosing. This is clearly highly undesirable. The present invention avoids these issues by surprisingly enhancing the solubility of zolpidem at relatively high concentrations in aqueous solution.

19. Accompanying this Declaration as Exhibit C is a table summarising some of the most important differences between zolpidem and ondansetron, including the differences in chemical structure.

20. Accompanying this Declaration as Exhibit D is a table summarising some of the most important differences between zolpidem and buprenorphine, including the differences in chemical structure.

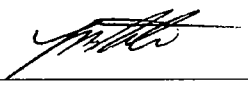
21. A person skilled in the art of drug delivery, would not, in my opinion, be able to reasonably predict the effect of cyclodextrins, including SBE-CD, and chitosans on zolpidem in view of the differences in structure and properties of ondansetron and buprenorphine.

22. After a reasonable computer search, I am not aware of any recognition of a compound called "chitosan hydroxycellulose" that is incidentally disclosed in Kramer, and do not believe that such a compound is known or exists.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present application or any patent issued thereon.

JONATHAN DAVID CASTILE

Dated: 12 Oct 2010



Curriculum Vitae: Jonathan Castile, MRPharmS, PhD

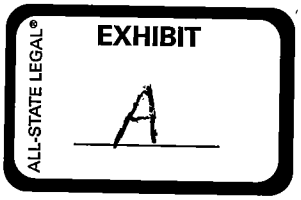
Career History

Jan. 2004 – Present	Formulation Group Head, Archimedes Development Ltd (formerly West Pharmaceutical Services), Nottingham, UK
Sep. 2001 – Jan. 2004	Lead Scientist, West Pharmaceutical Services
Jan. 2000 – Sept. 2001	Research Scientist, West Pharmaceutical Services
Jul.1994 – Jul. 1997	Phamacist / Manager (Sundays), Boots the Chemists, Oxford Street, London
Jul. 1994 – present	Consultant Pharmacist

Education and Qualifications

1994-1998 **PhD (Pharmaceutics):** The School of Pharmacy, University of London

1990-1993 **Pharmacy Degree:** The School of Pharmacy, University of London
BPharm (Hons), 1st Class honours.



Publications

2010 Morris GA, Castile JD, Smith A, Adams GC and Harding SE. The effect of different storage temperatures on the physical properties of pectin solutions and gels. *Polymer Degradation and Stability. In press.*

2010 Morris GA, Castile JD, Smith A, Adams GC and Harding SE. The effect of different storage temperatures on the stability of tripolyphosphate (TPP) – chitosan nanoparticles. *In preparation*

2009 Morris GA, Castile JD, Smith A, Adams GC and Harding SE. "The kinetics of chitosan depolymerisation at different temperatures" Polymer Degradation and Stability, 94, 1344-1348

2009 Morris GA, Castile JD, Smith A, Adams GC and Harding SE. "Macromolecular conformation of chitosan in dilute solution: a new global hydrodynamic approach" *Carbohydrate Polymers* 76 (2009) 616–621

2008 Morris GA, García de al Torre J, Castile JD, Smith A and Harding SE. "Molecular flexibility of citrus pectins by combined sedimentation and viscosity analysis." *Food Hydrocolloids*, 22, 1435-1442.

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1998 Castile JD. "The interaction of multilamellar and freeze-thawed liposomes with poloxamer surfactants" *PhD thesis. University of London,* November 1998.

1998 Castile JD, Taylor KMG and Buckton G. "The influence of poloxamer surfactants on the thermal pre-transition of DMPC and DPPC liposomes" *J. Pharma. Pharmacol.* 50 (suppl.), pp 147.

1996 Castile JD, Taylor KMG and Buckton G. "An investigation into the interaction between poloxamers and liposomes" *Pharm. Res.* 13, pp S165.

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THE
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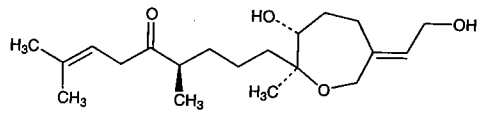
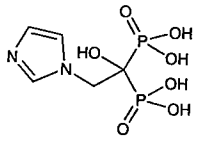
theses of (±)-form: R. Chen, D. A. Rowand, *J. Am. Chem. Soc.* **102,** 6609 (1980); K. C. Nicolau *et al., ibid.* 6611; V. V. Kane, D. L. Doyle, *Tetrahedron Letters* **22,** 3027, 3031 (1981). Mass spec: C. J. Shaw, *Org. Mass Spectrom.* **16,** 281 (1981). ^{13}C-NMR study: M. L. Cotter, *Org. Magn. Res.* **17,** 14 (1981).



Pale yellow oil.

10239. Zoledronic Acid. [118072-93-8]; [165800-06-6] (monohydrate). [1-Hydroxy-2-(1*H*-imidazol-1-yl)ethylidene]-bisphosphonic acid; 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid; CGP-42446. $C_5H_{10}N_2O_7P_2$; mol wt 272.09. C 22.07%, H 3.70%, N 10.30%, O 41.16%, P 22.77%. Bisphosphonate antiresorptive agent. Prepn: **JP Kokai 88 150291**; K. A. Jaeggi, L. Wilder, **US 4939130** (1988, 1990 both to Ciba-Geigy). Effect on bone metabolism: J. R. Green *et al., J. Bone Min. Res.* **9,** 745 (1994). Determn in plasma by enzyme inhibition assay: F. Risser *et al., J. Pharm. Biomed. Anal.* **15,** 1877 (1997). Clinical trial in tumor-induced hypercalcemia: J. J. Body, *Cancer* **80,** 1699 (1997). Series of articles on pharmacology and clinical experience: *Brit. J. Clin. Pract. Suppl.* **87,** 15-22 (1996).



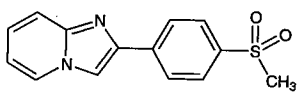
Crystals from water, mp 239° (dec).

Disodium salt tetrahydrate. [165800-07-7] Zoledronate disodium; CGP-42446A. $C_5H_8N_2Na_2O_7P_2.4H_2O$; mol wt 388.11.

Trisodium salt hydrate. [165800-08-8] Zoledronate trisodium; CGP-42446B. $(C_5H_7N_2Na_3O_7P_2)_5.2H_2O$; mol wt 1726.21.

THERAP CAT: Bone resorption inhibitor.

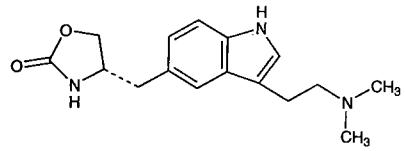
10240. Zolimidine. [1222-57-7] 2-[4-(Methylsulfonyl)-phenyl]imidazo[1,2-*a*]pyridine; zoliridine; Solimidin. $C_{14}H_{12}N_2O_2S$; mol wt 272.33. C 61.75%, H 4.44%, N 10.29%, O 11.75%, S 11.77%. Gastroprotective agent. Prepn: **GB 991589**; L. Almirante *et al.*, **US 3318880** (1965, 1967 both to Selvi); *eidem, J. Med. Chem.* **8,** 305 (1965). Metabolism: *eidem, Farmaco Ed. Sci.* **29,** 941 (1974). Series of articles on pharmacology: *Panminerva Med.* **16,** 301-359 (1974). Pharmacokinetics: E. Schraven, D. Trottnow, *Arzneimittel-Forsch.* **26,** 213 (1976). Clinical mucopoietic activity: S. Abate *et al., Int. J. Tiss. Reac.* **4,** 319 (1982); M. C. Parodi *et al., Scand. J. Gastroenterol.* **19,** Suppl. 92, 163 (1984). Clinical study: A. Materia *et al., Clin. Ter.* **97,** 183 (1981).



Crystals, mp 242-244°. LD_{50} orally in rats: 3710 mg/kg (Almirante, 1967).

THERAP CAT: Antiulcerative.

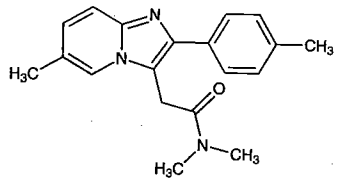
10241. Zolmitriptan. [139264-17-8] (4*S*)-4-[[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-2-oxazolidinone; (*S*)-*N,N*-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-3-yl]ethylamine; 311C90; BW-311C90; Zomig. $C_{16}H_{21}N_3O_2$; mol wt 287.36. C 66.87%, H 7.37%, N 14.62%, O 11.14%. Serotonin $5HT_{1D}$-receptor agonist. Prepn: A. D. Robertson *et al.*, **WO 91 18897** (1991 to Wellcome Foundation); *eidem,* **US 5466699** (1995 to Burroughs Wellcome). Structure-activity and receptor binding study: R. C. Glen *et al., J. Med. Chem.* **38,** 3566 (1995). Pharmacology: P. J. Goadsby, L. Edvinsson, *Headache* **34,** 394 (1994). Clinical pharmacokinetics: E. Seaber *et al., Brit. J. Clin. Pharmacol.* **41,** 141 (1996). Clinical trial in migraine: S. J. Tepper *et al., Curr. Med. Res. Opin.* **15,** 254 (1999).



White crystals from isopropanol as the 0.9 isopropanolate hemihydrate, mp 139-141°. $[\alpha]_D^{22}$ −5.79° (c = 0.5 in methanol). pKa 9.64. Stable; nonhygroscopic. Soly in aq soln at neutral pH: >20 mg/ml.

THERAP CAT: Antimigraine.

10242. Zolpidem. [82626-48-0] *N,N,*6-Trimethyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-acetamide; *N,N,*6-trimethyl-2-*p*-tolylimidazo[1,2-*a*]pyridine-3-acetamide; SL-80.0750. $C_{19}H_{21}N_3O$; mol wt 307.39. C 74.24%, H 6.89%, N 13.67%, O 5.20%. Selective benzodiazepine receptor agonist not related chemically to benzodiazepines. Prepn: J. P. Kaplan, P. George, **EP 50563**; *eidem,* **US 4382938** (1982, 1983 both to Synthelabo). Neuropharmacology: S. Arbilla *et al., Arch. Pharmacol.* **330,** 248 (1985); H. Depoortere *et al., J. Pharmacol. Exp. Ther.* **237,** 649 (1986). Neurochemical profile: B. Scatton *et al., ibid.* 659. Binding study in rat brain: S. Arbilla *et al., Eur. J. Pharmacol.* **130,** 257 (1986). HPLC determn in plasma: P. Guinebault *et al., J. Chromatog.* **383,** 206 (1986). Clinical evaluation of hypnotic activity: A. N. Nicholson, P. A. Pascoe, *Brit. J. Clin. Pharmacol.* **21,** 205 (1986). Evaluation as pre-anesthetic medication: J. N. Cashman *et al., ibid.* **24,** 85 (1987).



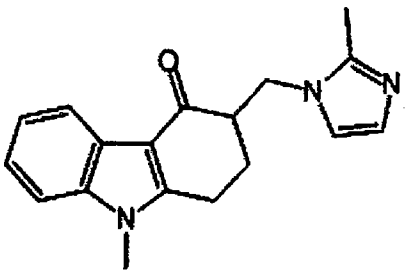
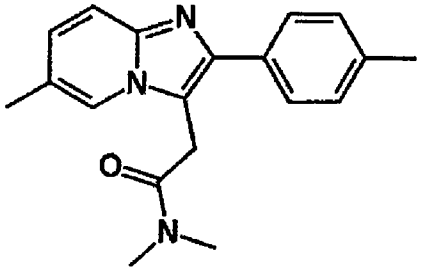
mp 196°. pKa 6.2.

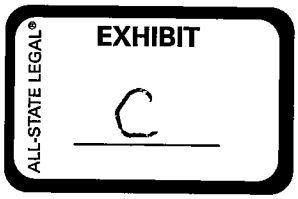
L-(+)-Hemitartrate. [99294-93-6] SL-80.0750-23N; Ambien; Ivadal; Niotal; Stilnoct; Stilnox. $(C_{19}H_{21}N_3O)_2.C_4H_6O_6$; mol wt 764.86. Soly in water (20°): 23 mg/ml.

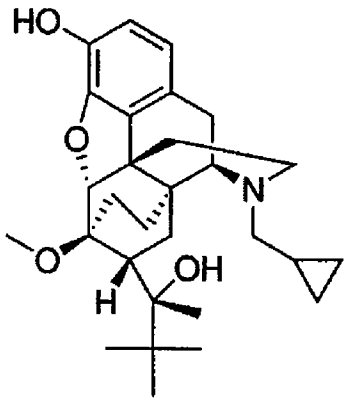
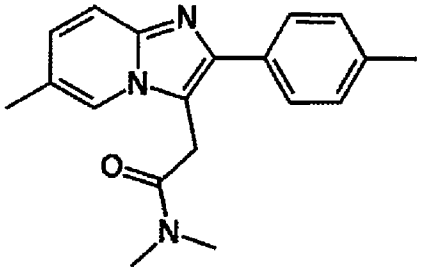
Note: This is a controlled substance (depressant): **21 CFR,** 1308.14.

THERAP CAT: Sedative, hypnotic.

10243. Zomepirac. [33369-31-2] 5-(4-Chlorobenzoyl)-1,-4-dimethyl-1*H*-pyrrole-2-acetic acid; 1,4-dimethyl-5-(*p*-chlorobenzoyl)pyrrole-2-acetic acid. $C_{15}H_{14}ClNO_3$; mol wt 291.73. C 61.76%, H 4.84%, Cl 12.15%, N 4.80%, O 16.45%. Prepn: J. R. Carson, **DE 2102746**; *idem,* **US 3752826** (1971, 1973 both to McNeil); J. R. Carson, S. Wong, *J. Med. Chem.* **16,** 172 (1973). Pharmacology: R. Sofia *et al., Pharmacol. Res. Commun.* **11,** 179 (1979); P. O'Neill *et al., J. Pharmacol. Exp. Ther.* **209,** 366 (1979). Determn in plasma by HPLC: K.-T. Ng, T. Snyderman, *J. Chromatog.* **178,** 241 (1979). Metabolism: J. M. Grindel *et al., Drug Metab. Dispos.* **8,** 343 (1980); W. N. Wu *et al., ibid.* 349. Pharmacokinetics: R. K. Nayak *et al., Clin. Pharmacol. Ther.* **27,** 395 (1980). Series of articles on pharmacology, kinetics, clinical studies: *J. Clin. Pharmacol.* **20,** 213-424 (1980). Preclinical narcotic abuse liability evaluation: J. H. Woods *et al., Arzneimittel-Forsch.* **33,** 218 (1983). Multicenter clinical study in painful conditions: C. E. Steele, W. L.

Name	Ondansetron	Zolpidem
Chemical structure		
Molecular weight	293.4 (base) 365.8(HCl salt)	307.4 (base) 764.9 (hemitartrate salt)
Solubility (water)	Approx. 10-33 mg/ml (HCl salt)	23 mg/ml (hemitartrate salt)
pKa	7.4	6.2
Therapeutic use	Nausea and vomiting	Sedative
Mode of action	Selective 5-HT3 receptor antagonist	Agonist at GABA receptors



	Buprenorphine	Zolpidem
Chemical structure		
Molecular weight	467.6 (base) 504.1 (HCl salt)	307.4 (base) 764.9 (hemitartrate salt)
Solubility	10-30 mg/ml (HCl salt)	23 mg/ml (hemitartrate salt)
pKa	8.4, 9.9	6.2
Therapeutic use	Analgesic	Sedative
Mode of action	Partial agonist at opiate μ receptors and antagonist at κ-receptors	Agonist at GABA receptors